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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/373,230	08/12/99	OKMURA H	OKAMURA=2E

EXAMINER	
JIANG,D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/373,230	OKMURA ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/505,535* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED OFFICE ACTION

Applicant's amendment in paper No. 5, and the terminal disclaimer in paper No. 6 filed on 05 April 2001 are acknowledged, entered or accepted. Following the amendment, claims 1-8 are amended, claim 10 is canceled, and the new claims 11-15 are added.

Currently, claims 1-9, and 11-15 are pending and under consideration.

Withdrawal of Objections and Rejections:

The objections of the specification are withdrawn in view of applicant's amendments.

The nonstatutory double patenting rejection of claims 1-2, and 7-10 is withdrawn in view of the terminal disclaimer in paper No. 6 filed on 05 April 2001, disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,912,324. The terminal disclaimer has been recorded.

The rejection of claims 1, 3-6, 8 and 9 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendments.

The rejection of claim 10 under 35 U.S.C. 112, second paragraph, as being indefinite is moot as the applicant has canceled the claim.

Formal Matters:

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the Examiner is unable to find the written description or definition in the specification for the term "IGIF" and "IL-18" in claims 1-3, 7, 11, and 12.

Additionally, the specification is objected to as using terminology, which is not generally accepted in the art and whose meaning cannot be determined. Specifically: "*antioncotic* agent" (page 3, line 17).

Further, the specification is objected to because of inconsistent use of SEQ ID Nos. The newly amended paragraph replacing the third paragraph at page 9 of the specification uses "SEQ ID NO:3" instead of SEQ ID NO:2 which was used in the previous version as indicated in the preliminary amendment in paper No. 2, filed on 12 August 1999. Clarification is required.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not pointed out, nor can the Examiner locate, the basis in the specification for the newly introduced recitation of "IGIF" and "IL-18" in these claims.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, and 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, and 11 are indefinite and vague for reciting "partial amino acid sequence possessing a part … of the amino acid sequence of SEQ ID NO:2, wherein Xaa is Met or Thr" in part (4) of the claims. It is unclear whether a part of SEQ ID NO:2 has to include the region where Xaa is, or any part of SEQ ID NO:2 is acceptable. Therefore, the metes and bounds of the claims cannot be unambiguously determined.

Claims 1-3, 7, 11, and 12 are indefinite for using parentheses, such as "(IGIF, IL-18)". It is unclear whether "IGIF, IL-18" in the parentheses is a part of the limitations of the claims, and if so, what limitation is imported by such as the terms are not defined by the specificaiton. See, for example, line 4 of claim 1.

The term "not substantially altering" in claims 3 and 11 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how much change in biological properties is "not substantially altering". Claim 11 is further indefinite because the specificity of said mAb can not be determined. Giving the broadest reasonable interpretation, said protein may have at least one amino acid, or as many as all amino acids (except two, to make a partial sequence of SEQ ID NO:2) replaced, which makes impossible to determine the epitopes for the mAb. Therefore, the metes and bounds of the claim cannot be unambiguously determined.

Claim 12 is indefinite because it is not clear what "IGIF" is, as no structural or functional limitation recited, and the specification does not definite such. The metes and bounds of the claimed protein, therefore, cannot be unambiguously determined merely upon an arbitrary name.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-6 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a specific variant of said protein, which has an amino acid sequence of SEQ ID:2 where residue 70 is methionine or threonine, does not reasonably provide enablement for with claims to variants having physicochemical and functional properties listed in parts (1) to (4) of claim 3, and having the amino acid sequence of SEQ ID NO:2 with at least one amino acid residue in SEQ ID:2 replaced with different amino acid, or at least one amino acid residue deleted or added to the N-terminus of SEQ ID:2 while not substantially altering physicochemical properties of the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants amendment, argument, and pointed out relevant contents in the specification have been fully considered, but they are not deemed persuasive because enablement is not commensurate in scope with claims to any or all possible proteins with physicochemical properties of (1) to (4) of claim 3. The specification discloses merely one amino acid sequence of SEQ ID NO:2 with two possible variations at Xaa. The claimed protein, given the broadest interpretation, reads on any or all proteins having said physicochemical and functional properties. With very limited sequence requirement, a protein having properties of (1) to (3) of claim 3, and comprising two amino acid sequence ("partial amino acid sequence") identical to SEQ ID NO:2, would meet the limitations of the claims. The specification has not taught how to make a commensurate number of such species.

Applicants argue that based the disclosures provided by the present specification and conventional genetic engineering techniques, a skilled person would have been able to obtain the "variant" without undue experiments. The disclosures pointed out by the applicants are related to "conventional genetic engineering techniques". However, in order to make such a sequence variant, for instance, with the reasonable assurance that it would meet all four limitations, the artisan would need to know which regions of the disclosed molecule are responsible for the interaction underlying its biological function(s), *and* which amino acid residues are responsible for keeping the same isoelectric point. As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. The disclosure does not teach the structural and functional relationship of the protein, and provides no guidance as to which regions of the protein would be tolerant of modification and which would not, or working examples of any variant sequence which would be within the limitations of the claims. It is in no way predictable that randomly selected mutations, deletions or additions, etc. in the disclosed sequence would afford a protein having activity and the physiochemical properties comparable to the one disclosed. As the specification does not teach how to make a number of species that would be commensurate in scope with the claims, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

Claims 1, 2, and 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a protein with SEQ ID NO:2, wherein residue 70 is methionine or threonine, does not reasonably provide enablement for variants with properties listed in these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1 and 2 are directed to a protein having physicochemical and functional properties listed in parts (1) to (3) of the claims, and with SEQ ID NO:2, or any *partial* sequence thereof. However, the specification does not identify which partial sequence of SEQ ID NO:2 is responsible for functional activity *and* physiochemical properties. For the same reasons addressed above, undue experimentation would be necessary to determine how to make the invention commensurate in scope with these claims.

Claim 11 is directed to a protein with SEQ ID NO:2, and variants thereof having properties listed in parts (1) to (4) of claim 11, and the variants react with a mAb specific to a protein or a variant of the protein having the amino acid sequence of SEQ ID NO:2 with at least one amino acid residue replaced (no upper limit), or at least one amino acid residue deleted or added to the N-terminus of SEQ ID NO:2. Enablement is not commensurate in scope with claims to any or all possible proteins with physicochemical and functional properties of (1) to (4) of claim 11, for the same reasons addressed above. In addition, the specification merely discloses one mAb, M-1 (Example 3), which reacts specifically with SEQ ID NO:2. The claim limitation of mAb, given the broadest interpretation, reads on mAbs direct against epitopes specific to SEQ ID NO:2, as well as any or all possible epitopes, which would include proteins of other kinds with the same physicochemical and functional properties, and without sequence similarity. The specification does not teach how to make a commensurate number of proteins, and therefore, it would require undue experimentation to determine the structural and functional relationship, and the specific epitopes required prior to making said protein species.

Claims 12 and 13 are directed to "an isolated protein of IL-18". As no structural limitations required, the claims read on IL-18 of any or all species, and biological equivalents thereof. The specification discloses merely *one* amino acid sequence with particularity, the murine IL-18 with SEQ ID NO:2, with two possible isoforms differing at a single amino acid

location, the residue 70 (Met^{70} and Thr^{70}). The specification does not teach any additional IL-18 from other species, or functional equivalents thereof. As no information on structural similarity of IL-18 among species is available in the prior art, or provided by the specification, a skilled artisan would not know how to make a "IL-18" of any kind.

Claims 14 and 15 are directed to a purified protein capable of inducing IFN-g production, and encoded by a DNA sequence which hybridizes to the oligonucleotide probe of SEQ ID NO:5 under low stringency (wash with 6X SSC). Given the fact of low hybridization stringency, and short oligonucleotide probe, DNA molecules encoding a functional equivalent (inducing IFN-g), and with local sequence similarity to SEQ ID NO:5 (17 nucleotides), but overall diverse sequence structures would hybridize to said probe under recited conditions. The specification provides no instruction or guidance as to how to make these variants.

Claims 1-6, and 11-15 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification discloses *one* amino acid sequence with particularity, the murine IL-18 with SEQ ID NO:2, and two possible isoforms differing at a single amino acid location, the residue 70 (Met^{70} and Thr^{70}). No other IL-18 variants or species meeting the limitations of these claims were ever identified or particularly described.

The present claims 1-6, 11, 14, and 15 encompass significant structural dissimilarity as compared to the exemplified IL-18, and the limitations which are positively recited have not been shown to correlate with the biological activity required by these claims. A skilled artisan would not be able to reasonably expect, for example, that a molecular weight of 19.5 kDa, a pI of

4.8, or a requirement for the presence of short subsequences affording *ca.* 30% overall identity with SEQ ID NO: 2 would correlate with the retention of biological properties characteristic of the murine IL-18 described in the disclosure. The Office therefore concludes that the two isoforms of SEQ ID NO: 2, differing by only a single amino acid, are not representative of all variants recited in claims 1-6, 11, 14, and 15, and thus that the disclosure does not convey to those skilled in the art that the inventors were in possession of the genera of variants of IL-18 at the time the application was filed.

Further, with respect to claim 11, the specification describes one mAb, M-1 (Example 3), which reacts specifically with SEQ ID NO:2. No other mAbs meeting the limitations of the claim (specific to any said variant) were ever identified or particularly described, and thus that the disclosure does not convey to those skilled in the art that the inventors were in possession of the genera of mAbs at the time the application was filed.

With respect to claims 12 and 13, the specification discloses *one* amino acid sequence with particularity, the *murine* IL-18 with SEQ ID NO:2, and two possible isoforms. However, the claims encompass *any* or *all* species of IL-18. It is thus generic to IL-18 with the broad structural limitation.

The broad genus claim is represented by *one* molecular species described with particularity in the disclosure, and no other species meeting the limitations of the claim is identified or particularly described. There is no evidence demonstrating the degree of structural or functional similarity or dissimilarity of IL-18 among species. The Examiner, therefore, concludes that the one species of IL-18 is not likely to be representative of all species recited in claim 12, and thus that the disclosure does not convey to those skilled in the art that the inventors were in possession of the genus of all IL-18 at the time the application was filed. Applicants assert that broader claims should be given to the inventors who first made such a pioneering invention. Such assertion is not found persuasive because IL-18 is only a member of interleukin family, and many members of this family were identified prior the invention of IL-18. Further, applicants have not disclosed what essential features define an IL-18 in a manner that supports the breadth of the claims.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, and 5-6 remain rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993; provided by the applicant). Applicants amended claims 3, which recites that the protein has a molecular weight of 19,000 + 5,000 daltons. Applicants argue that this is clearly different from Nakamura's molecular weight of 50-55 kDa on SDS-PAGE, and accordingly, the protein factor of Nakamura does not anticipate the claimed invention. Applicants amendment and argument have been fully considered, but is not deemed persuasive because in the subsequent study, Okamura et al. (Infection and Immunity, 1995, 63(10):3966-72) discloses a purified murine IGIF from the liver with the same physiochemical and biological properties as the claimed IGIF, and further indicates that the same molecule was also demonstrated in the serum factor that was previously reported (by Nakamura) to have an apparent molecular mass of 75 kDa by gel filtration (and 50-55 kDa on SDS-PAGE). Moreover, Okamura demonstrates that the molecular mass of 75 kDa IGIF was reduced to 19 kDa on 0.1% SDS-PAGE in the presence of DTT, and the N-terminal amino acid sequence is the same as that of IGIF from the liver, "thus IGIF in the serum sample was proved to be the same IGIF as that found in the liver exact "(the abstract, and page 3969, the second paragraph of the left column). Therefore, the protein factor of Nakamura anticipates the invention in claims 3, and 5-6. Additionally, a later publication from the same laboratory (Ushio *et al., J. Immunol.* 156: 4274-4279, 1996, provided by the applicants) evidences that the 18-19 kDa murine factor described by in the Okamura paper has an amino acid sequence (Fig. 2) which is identical to that shown in instant SEQ ID NO: 2. In view of the similar sources and the identity of structural, biophysical, and functional properties of the instantly claimed protein and the 18-19 kDa factor described in the Okamura and Ushio papers, it reasonably appears that they are the same.

Claims 1, 2, and 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993; provided by the applicant), as applied above.

The teachings of Nakamura was reviewed in the last office action. Additionally, Okamura proves that Nakamura's IGIF in the serum sample is the same IGIF as that found in the liver exact (see above). Therefore, Nakamura's IGIF inherently possesses the physiochemical and biological properties as listed in these claims, and meets the limitations in claims 1, 2, and 11-15. The reference, therefore, anticipates the invention in these claims.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

LORRAINE SPECTOR
PRIMARY EXAMINER

DJ
6/11/01